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ABSTRACT

Background The efficacy of external counterpulsation (ECP) on coronary collateral growth has not been investigated in a randomised controlled study.

Objective To test the hypothesis that ECP augments collateral function during a 1 min coronary balloon occlusion.

Patients and methods Twenty patients with chronic stable coronary artery disease were studied. Before and after 30 h of randomly allocated ECP (20 90 min sessions over 4 weeks at 300 mm Hg inflation pressure) or sham ECP (same setting at 80 mm Hg inflation pressure), the invasive collateral flow index (CFI, no unit) was obtained in 34 vessels without coronary intervention. CFI was determined by the ratio of mean distal coronary occlusive pressure to mean aortic pressure with central venous pressure subtracted from both. Additionally, coronary collateral conductance (occlusive myocardial blood flow per aorto-coronary pressure drop) was determined by myocardial contrast echocardiography, and brachial artery flow-mediated dilatation was obtained.

Results CFI changed from 0.125 (0.073; interquartile range) at baseline to 0.174 (0.104) at follow-up in the ECP group (p=0.006), and from 0.129 (0.122) to 0.111 (0.125) in the sham ECP group (p=0.14). Baseline to follow-up change of coronary collateral conductance was from 0.365 (0.268) to 0.568 (0.585) ml/min/100 mm Hg in the ECP group (p=0.072), and from 0.229 (0.212) to 0.305 (0.422) ml/min/100 mm Hg in the sham ECP group (p=0.45). There was a correlation between the flow-mediated dilatation change from baseline to follow-up and the corresponding CFI change (r=0.584, p=0.027).

Conclusions ECP appears to be effective in promoting coronary collateral growth. The extent of collateral function improvement is related to the amount of improvement in the systemic endothelial function.

INTRODUCTION

Cardiovascular disease is the leading cause of death in industrialised countries and may become the most important reason for mortality world wide.[1] In patients with coronary artery disease (CAD), the *size* of myocardial infarction mainly determines outcome after such an event.[2] Accordingly, it is the primary strategy to reduce cardiovascular mortality by shrinking infarct size. Infarct size is directly influenced by the following factors: duration of coronary occlusion, ischaemic area at risk for infarction, lack of collateral blood supply to the ischaemic zone, absence of ischaemic preconditioning before the infarct, myocardial oxygen consumption during the infarct.[3] Aside from curtailing coronary occlusion duration, the option of reducing infarct size by collateral artery growth promotion is appealing.

Collateral growth is triggered by increased tangential fluid shear stress at the endothelium, the product of spatial flow velocity changes during the cardiac cycle and blood viscosity.[4] Lower-leg, high-pressure external counterpulsation (ECP) triggered to occur during diastole induces a flow velocity signal and thus, tangential endothelial shear stress *in addition* to the flow signal caused by cardiac stroke volume. In this context and particularly because of the relevance of diastolic flow augmentation for the coronary circulation. ECP has been shown to improve myocardial blood flow and to ease related symptoms.[5] ECP has been repetitively *hypothesised* but not investigated in a randomised controlled fashion with regard to coronary arteriogenesis.[5–7]

Therefore, the goal of this study in patients with chronic stable CAD was to test the hypothesis that ECP improves collateral function.

METHODS

Patients

Twenty patients with chronic stable one- (n=3), two- (n=9) or three-vessel (n=8) CAD (stable, exercise- or stress-induced angina pectoris) eligible for percutaneous coronary intervention (PCI) of at least one stenotic lesion were included in the study. All underwent diagnostic coronary angiography because of symptoms related to CAD. Patients were prospectively selected on the basis of the following criteria: (1) no previous transmural infarction in the myocardial areas assessed for coronary collaterals, (2) normal left ventricular ejection fraction, (3) no congestive heart failure, (4) no baseline ECG ST-segment abnormalities, (5) no aortic regurgitation, (6) no lower-leg deep vein thrombosis as assessed by duplex sonography, (7) no atrial fibrillation or frequent supraventricular or ventricular beats. Patients were randomly assigned to lower-leg, high-pressure (300 mm Hg cuff inflation pressure; **ECP group**, n=10) or low-pressure (80 mm Hg cuff inflation pressure; **sham ECP group**, n=10) ECP treatment with a total of 20 90 min sessions (=30 h; 5 days a week, 4 weeks). The randomisation scheme in two block sizes of 10 was generated using the website Randomization.com (http://www.randomization.com, accessed November 2009) before the study began, whereby a study nurse, but not the investigators performing the study measurements and data analyses, were aware of the

randomisation key. Collateral function and absolute myocardial perfusion were assessed during balloon occlusion in a stenotic and, if possible, in an angiographically and functionally normal coronary artery at baseline before and immediately after the treatment period.

This investigation was approved by the institutional ethics committee, and the patients gave written informed consent to participate in the study.

Cardiac catheterisation and coronary angiography

Patients underwent left heart catheterisation for diagnostic purposes from the right femoral approach. Aortic pressure was measured using a 6F PCI guiding catheter. Central venous pressure (CVP) was obtained via the right femoral vein. Left ventricular end-diastolic pressure was determined before PCI. Biplane left ventriculography was performed followed by biplane coronary angiography. Coronary artery stenoses were determined quantitatively as percentage diameter narrowing (>50% diameter reduction being a relevant stenosis severity).

Invasive coronary assessment

Primary study end point

Coronary collateral flow relative to normal antegrade flow through the non-occluded coronary artery (collateral flow index, CFI) was determined using coronary pressure measurements. A 0.014 inch pressure monitoring angioplasty guidewire (Pressure Wire, Radi, Uppsala, Sweden) was set at zero, calibrated, advanced through the guiding catheter and positioned in the distal part of the vessel of interest. CFI was determined by simultaneous measurement of mean aortic pressure (P_{ao}, mm Hg), distal coronary artery pressure during balloon occlusion (P_{occl}, mm Hg), and the CVP (mm Hg). CFI was calculated as (P_{occl}−CVP) divided by (P_{ao}−CVP).[8 9]

Secondary study end points

Absolute myocardial perfusion or blood flow at rest and during hyperaemia was assessed quantitatively using myocardial contrast echocardiography (MCE; Acuson Sequoia 512, Acuson Siemens, Mountain View, California, USA), whereby a previously described and validated algorithm was employed.[10] Briefly, for the calculation of absolute blood flow, the constituent factors, relative myocardial blood volume rBV and its refill rate β following destruction of echo contrast microbubbles, were obtained during vessel patency. Myocardial blood flow is equal to the product of rBV and β divided by myocardial tissue density.[10] Absolute myocardial blood flow at rest was also determined during coronary occlusion, thereby allowing the calculation of coronary collateral conductance (myocardial blood flow/(P_{ao}−P_{occl}) in ml/min/100 mm Hg).

As a parameter characterising the functional influence of the added shear rate signal by ECP on the circulation, right brachial artery flow-mediated vasodilatation (FMD) was determined before and after ECP treatment by two-dimensional vascular ultrasound imaging.[11]

Study protocol

FMD measurement was performed while fasting before and after ECP treatment (before PCI) during a session separate from the invasive procedure.

At the start of both baseline and follow-up invasive procedures, all patients received 5000 units of heparin intravenously. Following diagnostic examinations, two puffs of oral isosorbide dinitrate were given. The coronary artery regarded as the lesion responsible for the patient's symptoms—that is, the one with the most severe stenosis, was selected for CFI measurements. This vessel underwent PCI *following* ECP treatment. Additionally, and if suitable, an angiographically and functionally normal coronary artery was selected for CFI measurement (normal vessel). In both arteries, fractional flow reserve was determined for functional assessment with the pressure guidewire positioned distally in the vessel using a bolus of intracoronary adenosine (12 μg for the right, 18 μg for the left coronary artery) for induction of hyperaemia. At baseline and follow-up, an adequately sized angioplasty balloon catheter (10–20 mm in length, diameter ranging from 2.5 to 4 mm) was positioned proximal to the stenosis to be dilated, and at a proximal location in the normal vessel, while the pressure guidewire was positioned distally in the respective vessels. Balloon inflation for collateral measurement before ECP treatment occurred in the proximal, non-stenotic vessel segment at a pressure of 1–2 atmospheres. During this vessel occlusion, simultaneous P_{occl}, P_{ao} and CVP were obtained for the calculation of CFI. The initial invasive procedure was followed by 30 h of ECP treatment at high or low cuff inflation pressure starting the day after the baseline procedure. The patients and the investigators performing the study measurements and data analyses were blinded to the ECP study group assignment (ECP sessions performed by a study nurse). All drugs were left unaltered during the study period. The invasive follow-up examination immediately after the treatment period consisted of intracoronary measurements identical to those described above. PCI of the stenotic lesion initially selected for dilatation was performed immediately after the follow-up measurements.

Absolute myocardial blood flow at rest and during hyperaemia in the areas supplied by the coronary arteries of interest was obtained using contrast echocardiography at baseline and at follow-up simultaneously with the invasive procedures. Hyperaemia was induced by intravenous adenosine (140 μg/min/kg), and myocardial perfusion reserve was calculated as absolute blood flow during hyperaemia divided by blood flow at rest (both in ml/min/g). In addition, myocardial blood flow at rest was also obtained during coronary occlusion simultaneously with the CFI measurement.

Statistical analysis

Sample size calculation was based on the assumption of detecting an increase during follow-up in CFI of at least 50% in the ECP group as compared with the sham ECP group. At a statistical power of 80%, the number of *vessels* to be measured was estimated to be 30. Since in the majority of patients, CFI would be obtainable in >1 vessel, the number of *patients* estimated to be included in the study was 20.

Continuous data are given as median and interquartile range. Baseline characteristics between the groups were analysed by a Mann–Whitney U test for continuous data and by χ^2/ Fisher's exact tests for categorical data. Within-group analyses at different time points were performed by a Wilcoxon signed rank test. Between-group comparison of treatment-induced changes of continuous end points was performed by a Mann–Whitney U test. Linear regression analysis was used for the comparison of ECP-induced CFI changes and corresponding FMD changes. Continuous values are given as median and interquartile range. Differences were considered statistically significant at a two-sided p value of <0.05. Statistical analysis was performed using StatView Version 4.57.

RESULTS

Patient characteristics and clinical data at baseline

The two groups had similar key baseline characteristics, such as age, gender, cardiovascular risk factors and cardiovascular medication (table 1).

Table 1 Patient characteristics at baseline

Variable	ECP (n=10)	Sham ECP (n=10)	p
Age (years)	61±12	65±5	0.402
Male gender	9 (90%)	8 (80%)	0.531
Duration of angina (months)	6.2±8.6	10.8±16.8	0.45
Angina pectoris CCS class 0/I/II/III	0/6/4/0	0/5/5/0	0.85
History of prior myocardial infarction (%)	5 (50%)	3 (30%)	0.36
Body mass index (kg/m^2)	29.0±4.8	28.1±5.7	0.728
Cardiovascular risk factors			
Systemic hypertension	6 (60%)	6 (60%)	1
Smoking	2 (20%)	1 (10%)	0.531
Cumulative pack years	12.5	18.5	0.480
Hypercholesterolaemia	8 (80%)	10 (100%)	0.136
Family history of coronary artery disease	5 (50%)	2 (20%)	0.160
Obesity (BMI >30 kg/m^2)	4 (40%)	3 (30%)	0.639
Diabetes mellitus	2 (20%)	1 (10%)	0.531
Blood chemistry values			
Total cholesterol (mmol/l)	4.2±1.0	5.1±1.1	0.114
Low-density lipoprotein cholesterol (mmol/l)	2.5±0.8	3.0±0.9	0.192
High-density lipoprotein cholesterol (mmol/l)	1.1±0.3	1.2±0.2	0.502
Triglycerides (mmol/l)	2.1±1.5	2.5±1.9	0.644
Creatinine (mmol/l)	76±15	77±13	0.875
Fasting glucose (mmol/l)	6.7±0.5	5.9±0.5	0.418
Medication			
Acetylsalicylic acid	9 (90%)	10 (100%)	0.305
Clopidogrel	6 (60%)	3 (30%)	0.178
β Blockers	7 (70%)	4 (40%)	0.178
Calcium channel blockers	0 (0%)	0 (0%)	
Nitrates	2 (20%)	2 (20%)	1
Statins	10 (100%)	9 (90%)	0.305
ACE inhibitors	5 (50%)	5 (50%)	1
Angiotensin receptor blockers	3 (30%)	3 (30%)	1

BMI, body mass index; CCS, Canadian Cardiovascular Society; ECP, external counterpulsation.

Invasive and haemodynamic data at baseline

Haemodynamic and angiographic data at baseline—that is, systemic blood pressure, heart rate, left ventricular ejection fraction and end-diastolic pressure, the structural and functional (fractional flow reserve) severity of CAD were not significantly different between the groups (table 2).

The stenotic and the normal vessels undergoing CFI measurement as well as the CFI measurement site were similarly distributed between the groups. CFI values at baseline did not differ significantly (table 2). Right brachial artery diameter was 4.1 (1.1) mm in the ECP group and 4.0 (1.3) mm in the sham ECP group (p=0.44). Right brachial artery flow-mediated dilatation was 4.3% (1.5) in the ECP group and 6.0% (3.0) in the sham ECP group (p=0.14). Myocardial blood flow reserve at baseline as determined by MCE was 1.51 (0.96) in the ECP group and 1.26 (1.99) in the sham ECP group (p=0.56).

Treatment-induced changes of study end points

Primary study end points

CFI values as obtained in 34 normal and stenotic vessels changed from 0.125 (0.073) at baseline to 0.174 (0.104) at follow-up in the ECP group (n=15; p=0.006), and from 0.129 (0.122) to 0.111 (0.125) in the sham ECP group (n=19; p=0.14; figure 1). CFI values as obtained in the stenotic vessels of the 20 patients changed from 0.098 (0.102) at baseline to 0.173 (0.071) at follow-up in the ECP group (p=0.003), and from 0.129 (0.164) to 0.109 (0.090) in the sham ECP group (p=0.121). The absolute change in CFI from baseline to follow-up as obtained in all vessels amounted to +0.069 (0.128) in the ECP group and to −0.017 (0.049) in the sham ECP group (p=0.0009). The respective numbers in the 20 study patients focusing on stenotic vessels were +0.104 (0.095) in the ECP group and −0.034 (0.122) in the sham ECP group (p=0.001).

Table 2 Invasive data at baseline

Variable	ECP (n=10)	Sham ECP (n=10)	p
Haemodynamic and angiographic data			
Systolic blood pressure (mm Hg)	125 (29)	134 (25)	0.45
Diastolic blood pressure (mm Hg)	73 (20)	72 (10)	0.80
Mean aortic blood pressure (mm Hg)	88 (12)	99 (17)	0.029
Heart rate (beats/min)	69 (14)	68 (16)	0.87
Left ventricular ejection fraction (%)	59 (15)	58 (8)	0.98
Left ventricular end-diastolic pressure (mm Hg)	10.5 (4.8)	11.9 (8.0)	0.81
Number of vessels diseased	2 (1)	2 (1)	0.72
Number of stenoses	2 (2)	2 (2)	0.52
Percentage diameter stenosis of treated vessel	65 (79)	50 (75)	0.73
Fractional flow reserve (no unit)	0.85 (0.19)	0.88 (0.11)	0.52
Collateral function data	15 arteries in 10 patients	19 arteries in 10 patients	
Stenotic vessels for CFI measurement (LAD/LCX/RCA)	7/0/3	6/3/1	0.32
Normal vessels for CFI measurement (LAD/LCX/RCA)	1/2/2	4/4/1	0.41
CFI measurement site (proximal/mid)	14/1	18/1	0.86
CFI (no unit)	0.125 (0.073)	0.129 (0.122)	0.90

Data are given as median (interquartile range) for continuous variables.
CFI, collateral flow index; ECP, external counterpulsation; LAD, left anterior descending artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

Secondary study end points

MCE-derived myocardial blood flow reserve in the region subtended by the vessels in which CFI was obtained changed from 1.51 (0.96) at baseline to 2.06 (1.22) in the ECP group (p=0.11), and from 1.26 (1.99) at baseline to 2.11 (2.95) in the sham ECP group (p=0.40). Resting coronary collateral conductance as obtained by MCE during vessel occlusion increased from 0.365 (0.268) at baseline to 0.568 (0.585) ml/min/100 mm Hg at follow-up in the ECP group (p=0.072), and from 0.229 (0.212) at baseline to 0.305 (0.422) ml/min/100 mm Hg at follow-up in the sham ECP group (p=0.45; figure 2). Right brachial artery FMD increased from 4.3% (1.5) at baseline to 6.9% (3.5) at follow-up in the ECP group (p=0.018), and from 6.0% (3.0) at baseline to 7.6% (3.5) at follow-up in the sham ECP group (p=0.10). The absolute change in FMD from baseline to follow-up as obtained in all vessels amounted to +1.75% (2.8) in the ECP group and to +0.50% (1.0) in the sham ECP group (p=0.07). There was a direct correlation between the FMD change from baseline to follow-up and the corresponding CFI change (p=0.0273; figure 3).

In the ECP group, fractional flow reserve increased from baseline to follow-up from 0.85 (0.13) to 0.91 (0.07) (p=0.05), whereas it changed from 0.88 (0.07) at baseline to 0.87 (0.04) (p=0.45).

DISCUSSION

This randomised controlled clinical study in patients with chronic stable CAD documents that ECP improves collateral function to a briefly occluded vessel. The level of CFI improvement in response to ECP treatment is directly related to the induced change of endothelium-dependent brachial artery dilatation.

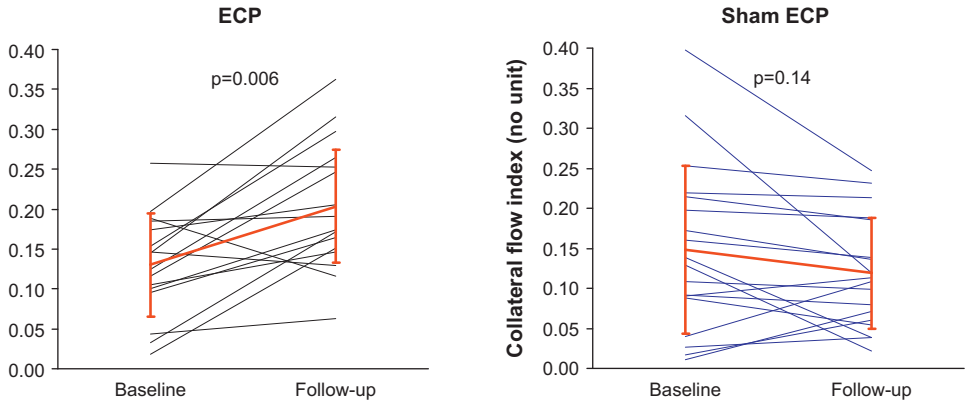

Figure 1 Individual changes of collateral flow index (vertical axes) from baseline to follow-up measurement in response to external counterpulsation (ECP; left panel; black lines) and to sham ECP (right panel; red lines). Red lines indicate mean values±SD.

Current therapeutic indications for ECP

More than half a century ago, Kantrowitz described diastolic augmentation of aortic perfusion pressure as a way to increase coronary blood flow.[12] Diastolic pressure augmentation by ECP at a pressure of 300 mm Hg results in an increase in diastolic and mean aortic and coronary pressure, a decrease in systolic pressure and an increase in coronary Doppler flow velocity.[13] So far, there has been only one controlled clinical trial investigating the effect of ECP versus sham ECP, showing a benefit of the former on the severity of angina pectoris, on the use of glyceryl trinitrate, on physical exercise capacity, and on the time to ECG ST-segment depression during exercise;[14] myocardial perfusion was not obtained in that study. More than a dozen other studies on the same subject have employed an uncontrolled design.[5] Accordingly, the European Society of Cardiology views ECP as a promising modality with more clinical trials needed to define its role in treating refractory angina pectoris.[15] Masuda and coworkers[6] sought to elucidate the mechanism by which ECP exerts its beneficial effects on chronic angina pectoris. Using [^{13}N] ammonia positron emission tomography, they found in 11 patients undergoing 35 1 h sessions of ECP that myocardial perfusion at rest and in response to dipyridamole was increased at the end of the treatment (myocardial blood flow reserve change from 1.75±0.24 to 2.08±0.28).[6] Myocardial blood flow reserve in response to ECP serves as an 'anchor' parameter for comparison in the context of our study, in which a numerically similar, but insignificant increase was found in the ECP group. In the study by Masuda *et al*,[6] an augmented coronary collateral circulation aside from reduced ventricular after load has been hypothesised to play *the* central role in the mechanism, whereby ECP exerts its benefits. However so far, the collateral or arteriogenesis hypothesis has never been tested in a randomised controlled trial. Very recently, Buschmann *et al* performed an uncontrolled investigation in patients with CAD who were initially allocated to ECP and later to a control group without ECP.[7] Patients in the ECP group showed a significant increase in coronary pressure-derived CFI; there was no change in CFI in the control group. Also similar to our study, fractional flow reserve increased in the ECP group but not in the control group.

Our study verifies the positive effect of ECP on the coronary collateral circulation in several ways. The primary study end point, CFI, improves in response to ECP in an unexpected magnitude, in comparison with other forms of coronary collateral growth promotion in humans (eg, colony stimulating factors[16 17]). Coronary collateral conductance—that is, *the* reference parameter describing tissue perfusion in experimental studies, is augmented likewise in the ECP group. Collateral conductance obtained by MCE was measured independently of, and simultaneously with, the invasive CFI assessment. In a clinical study, this is unique and unprecedented, because other modalities to obtain absolute tissue perfusion in humans do not allow such measurements to be performed during a brief artificial coronary balloon occlusion. Myocardial blood flow reserve as obtained during vessel patency and before PCI, and thus representing changes in collateral flow, points in the same direction.

Underlying pathogenetic principle of *physical* collateral growth promotion

Since fluid shear stress, the trigger of arteriogenesis, is the product of the spatial flow velocity change between different fluid layers (dv/ds=shear rate) and the blood viscosity, and because the latter can be regarded as remaining constant over the course of 4 weeks, the focus with regard to physical forms of collateral growth is on the amplitude, duration and number of flow velocity signals per cardiac cycle operative at the

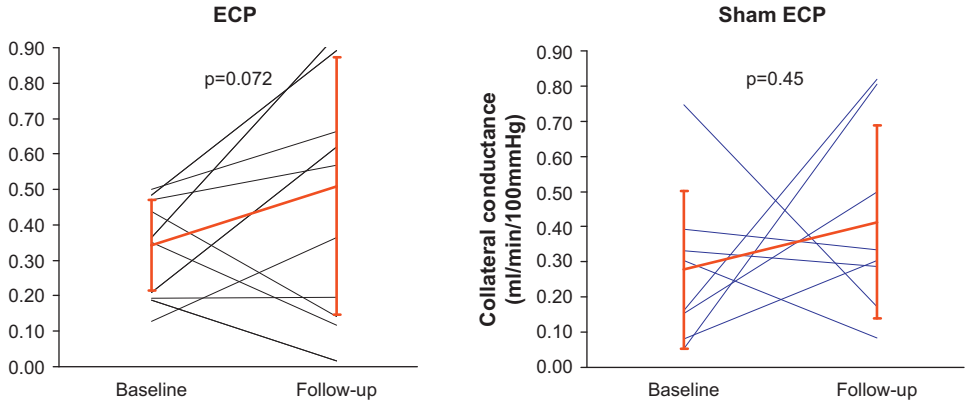

Figure 2 Individual changes from baseline to follow-up of coronary collateral conductance as obtained during vessel occlusion and by myocardial contrast echo (vertical axes) in response to external counterpulsation (ECP; left panel; black lines) and to sham ECP (right panel; red lines). Red lines indicate mean values±SD.

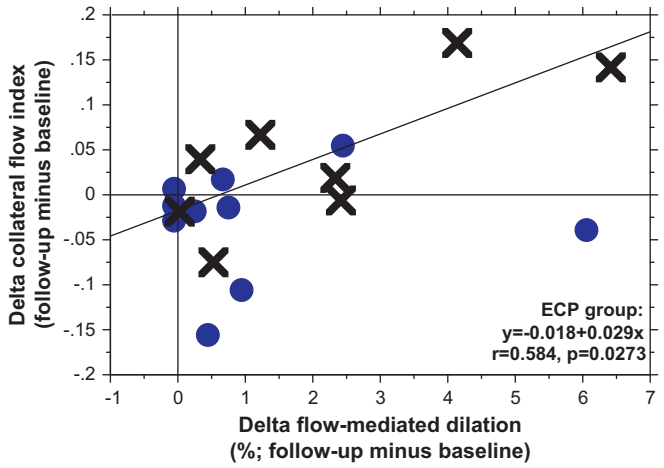

Figure 3 Correlation between the change during follow-up in brachial artery flow-mediated dilatation (horizontal axis) and the corresponding change in collateral flow index (vertical axis). Cross symbols: external counterpulsation (ECP) group; blue dots: sham ECP group.

endothelium. Hence, the following classes of physical collateral growth promotion can be distinguished: increased cardiac output (augmented flow rate with a respective increase in flow velocity), extended duration of diastole and added number of diastolic flow velocity signals. Both endurance exercise training respectively ECP treatment can be categorised accordingly as temporary and repetitive increase in cardiac output, respectively, added shear rate signals. Alternatively, the prolonged diastole at rest induced by the training could be responsible for the arteriogenic effect of physical exercise. For the sake of the argument, the term arteriogenesis can be used in a broader sense than collateral growth promotion—namely, as general arterial calibre growth. In the latter context, there have been a number of studies confirming the concept of 'arteriogenesis' in response to augmented shear rate—for example, through exercise training.[18 19] Similarly, the added shear rate signal during diastole with ECP is probably responsible for its arteriogenic effect. Two related questions arising in the context of this study are: does the diastolic shear rate signal present also in the sham ECP group have an amplitude insufficient to induce collateral growth? and do we have data from this study supporting the arteriogenic mechanism operative in ECP just alluded to? Regarding CFI, the diastolic low-velocity signal caused by the 80 mm Hg inflation pressure sham ECP appears to be inadequate to augment collateral function. However, and with respect to brachial artery FMD, there is a trend towards improved endothelial function in the sham ECP group. Is brachial artery FMD an adequate marker to support the hypothesised mechanism of augmented fluid shear stress by which ECP induces arteriogenesis?

FMD is a parameter of arterial endothelial *function*, whereas arteriogenesis is primarily a *structural* process resulting in functional improvement of arterial conductance. However, vasodilatation is the first step in the pathogenesis of collateral growth and occurs in response to augmented tangential shear stress owing to an increased pressure gradient between the source of preformed collaterals and their orifice in the stenotic epicardial artery. Accordingly, the necessary condition for arteriogenesis induced by augmented vascular shear stress, improved endothelial function, could be observed in a circulatory region remote from the coronary arteries using a method which allowed also the visualisation of the added flow velocity signal caused by ECP. More importantly, our study revealed a direct association between ECP-induced improvement in brachial artery endothelial and coronary collateral function. The functional parameter of myocardial blood flow reserve, a parameter obtained in this study by myocardial contrast echo behaved similar to FMD without reaching statistical significance.

Study limitations

The main limitation of this study is its small sample size. Thus, despite the unexpectedly marked effect of ECP on collateral function, the findings should be interpreted as proof of concept that ECP might promote coronary collateral growth rather than definite evidence of efficacy. Data are even more limited with regard to the secondary end point of FMD.

The principal explanation for the incomplete agreement between contrast-echo-derived myocardial blood flow reserve and FMD, respectively, between collateral conductance and CFI is mainly related to the difficult examination conditions for transthoracic echocardiography with the patient lying on his back on the catheterisation laboratory table. In comparison with the usual left lateral supine position, respiratory artefacts impair the ultrasound image quality much more in the supine back position.

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Competing interests None.

Ethical approval This study was conducted with the approval of the Kantonale Ethikkommission Bern, Switzerland.

Provenance and peer review Not commissioned; externally peer reviewed.

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